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Review

Mesenchymal Stem/Stromal Cells: A Review for Its Use After Allogeneic Hematopoietic Stem Cell Transplantation

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Abstract

Mesenchymal stem/stromal cells (MSCs) exhibit broad differentiation capability and strong immunoregulatory potential mediated through intercellular communication and the release of diverse paracrine mediators. These features render MSCs a promising therapeutic option for managing complications associated with allogeneic hematopoietic stem cell transplantation (allo-HSCT). This review provides an updated synthesis of MSC biology, their bidirectional interaction with immune cells, and their functional contribution to the hematopoietic niche. It also evaluates current clinical evidence regarding the therapeutic roles of MSCs and MSC-derived extracellular vesicles (EVs) in acute and chronic graft-versus-host disease (aGVHD/cGVHD) as well as in poor graft function. Mechanistic insights encompass macrophage polarization toward an anti-inflammatory phenotype, inhibition of dendritic cell maturation, enhancement of regulatory T-cell expansion, and modulation of cytokine signaling pathways. Within the bone marrow milieu, MSCs contribute to stromal restoration and angiogenic repair. Data from phase II/III clinical trials and real-world cohorts in steroid-refractory aGVHD consistently confirm the safety of MSC therapy, although response rates vary—typically higher in pediatric patients and when administered early—while survival outcomes remain inconsistent. For poor graft function, limited prospective studies indicate hematopoietic recovery following third-party MSC infusions, and combination approaches such as co-administration with thrombopoietin receptor agonists are under investigation. MSC-derived EVs emulate many immunomodulatory effects of their parental cells with a potentially safer profile, though clinical validation remains in its infancy. MSC-oriented interventions hold substantial biological and therapeutic promise, offering a favorable safety margin; however, clinical translation is hindered by product variability, suboptimal engraftment and persistence, and inconsistent efficacy across studies. Future directions should emphasize standardized manufacturing and potency assays, biomarker-driven patient and timing selection, optimized conditioning and dosing strategies, and the systematic appraisal of EV-based or genetically modified MSC products through controlled trials.

Keywords: mesenchymal stem/stromal cells; allogeneic hematopoietic transplantation; graft-versus-host disease; poor graft function; extracellular vesicles; immune modulation

1. Introduction

MSCs were initially defined in the late 1960s as bone marrow (BM) cells, having fibroblast-like morphology, with self-renewal capability [1]. Subsequent studies also demonstrated that MSCs were able to differentiate into several lineages, such as epithelial, neuronal, astrocytic, endothelial, and smooth muscle cells in vitro, in a coculture fashion with different cell types when subjected to characterizing conditions [2–7]. Furthermore, MSCs can differentiate into other cell lineages for the

enhancement of inflammatory reactions [8]. These mirror the MSCs' role of maintaining tissue homeostasis and improving structural integrity.

Given their MSCs' potent immunomodulatory capacity, plasticity and self-renewal ability they have started to find space in various treatment schemes for wide array of disorders. MSCs mediate potent immunomodulatory effects via direct cell–cell contact and through release of bioactive molecules that regulate both innate and adaptive immune cells [9]. In the bone marrow, MSCs at various stages of maturation constitute the hematopoietic stem cell (HSC) niche and have an important function in HSCs maintenance and renewal [10]. These findings pave the way for using MSCs in acute graft-versus-host disease (aGVHD) and graft failures after allogeneic HSC transplants, which constitutes the major fields for MSC treatment in malignant hematology [11,12]. Survival and homing issues are the major drawbacks for the MSC treatment, thus optimizing the conditioning protocols and maintaining the intact paracrine signaling should be the first priorities mainly in the context of HSC transplantation [13].

MSC-Derived Extracellular Vesicles (MSC-EVs), offer some therapeutic potential like their parental cells. MSC-EVs contain exosomes (30–120 nm, secreted from multivesicular endocytic structures), macrovesicles (100–1000 nm, from the plasma membrane), and apoptotic bodies [9]. They control immune responses by inhibiting Th17 differentiation and induce peripheral tolerance through PD-L1 and PD-L2. There is some evidence about the use of exosomes in human disease, others are ongoing [14–16].

In this review, we aimed to review the relevant literature about MSC biology and its interactions with the immune system and other tissues with a special attention to HSC and bone marrow microenvironment. Also, therapeutic uses of MSCs were summarized.

2. Mesenchymal Stem Cell: Origin, Biology and Functions

The discovery of MSCs can be traced back to the mid-1970s, when fibroblast-like adherent cells were first isolated from bone marrow and shown to form colony-forming units capable of differentiating into osteogenic lineages and supporting hematopoietic growth [17]. This foundational finding established the concept of bone marrow–derived stromal cells as a distinct progenitor population. Subsequent studies demonstrated that these stromal cells retained their osteogenic potential even after extensive passaging, and by the late 1980s, they were recognized for their ability to generate bone and cartilage tissue *in vivo*, underscoring their multilineage differentiation capacity [17]. A major conceptual shift occurred in 1991, when the term *mesenchymal stem cell* was coined to describe these multipotent cells of mesodermal origin. This marked the formal recognition of MSCs as a self-renewing stem cell population distinct from fibroblasts, despite their similar morphology *in vitro* [18]. Many studies are using the given nomenclature in recent years.

International Society for Cellular Therapy has defined the immunophenotype of MSC [19]. Based on this definition, the cell surface markers CD73, CD90 and CD105 should be exhibited while CD14, CD34, CD45, CD11b, CD79, and histocompatibility complex molecule HLA-DR should be lacking [19]. Additionally, cell culture conditions and transforming capabilities of MSCs were addressed [19].

MSCs perform vital functions in destroyed tissue repair by immunosuppressive, antiapoptotic, anti-inflammatory, antifibrotic, pro-angiogenic, antitumorigenic, neuroprotective, antibacterial, and chemo attractive activities [20]. MSCs are expanded within the marrow microenvironment and received signals which specify their fate. These signals include cell-to-cell interactions, cell-to-matrix interactions and transcriptional program that activates and/or suppresses MSC genes [21].

In addition to their multipotency, MSCs have immunomodulatory activities that have been studied as a therapy for several immune-related diseases. They mediate potent immunomodulatory effects via direct cell–cell contact and through release of bioactive molecules that regulate both innate and adaptive immune cells [9]. Additionally, MSCs do not express human leukocyte antigen (HLA) Class II and can be administered without needing to match donors to recipients. This

immunomodulatory phenotype enables MSCs to be used from one donor to various recipients without immune-mediated rejection [9,19].

2.1. Interactions with Immune System Cells

Preclinical data suggest that MSCs control the innate and adaptive immune response with direct interaction with T cells, B cells, neutrophils, monocytes, macrophages, NK cells, and DCs, displaying broad immunomodulatory effects by cell-to-cell contact and paracrine action [22–24]. MSCs predominantly control macrophages by secreting soluble factors [25]. Through the production of PGE2, TGF- β , and CCL2, MSCs can induce polarization of macrophages from the pro-inflammatory M1 phenotype toward the anti-inflammatory M2 phenotype [26].

IL-17 from MSCs may activate neutrophils and enhance their phagocytic activity. MSCs obtained from bone marrow decrease the release of reactive oxygen species (ROS) from activated neutrophils and those isolated from umbilical cord tissue dampen the neutrophil-associated inflammation [27].

MSC decreases the differentiation, maturation, and antigen-presenting function of Dendritic cells (DCs) with consequent reduction in pro-inflammatory cytokines. Furthermore, MSCs block the generation of immature DCs and impair CD34+ precursor differentiation into epidermal DCs [28].

By keeping macrophages and DCs in an immature or anti-inflammatory state, MSCs reduce the activation of effector T cells and favor the generation of regulatory T (Treg) cells [29,30]. Regulatory T cells (Tregs), a sub-population of CD4+ T cells that express Forkhead box P3 (FoxP3) and CD25 (IL-2 receptor) on their surface, have strong immunosuppressive and anti-inflammatory activities [31]. MSCs might also drive the expansion and differentiation of Tregs via an HLA-G5-dependent mechanism by the PGE2 and TGF- β 1 released from MSCs, and IL-10 secreted by Th2 cells [32]. MSC may also induce CD4(+) T cell towards Tregs by Notch-1 signaling. Notch1/FoxP3 pathway is also activated in CD4+ T cells co-cultured with MSCs, which promotes the percentage of CD4+CD25^{high}FoxP3+ Tregs [33,34]. Blockade of TGF- β as well as IL-10 abolishes the induction of Treg, emphasizing their crucial roles in immune tolerance [34].

Captivatingly, galectin-1, is expressed mostly in MSCs where it regulates cytokine secretion in GvHD and autoimmunity. Suppression of galectin-1 reverts immunosuppression of MSCs on allo-immune T cells by rescuing responses of CD4+ and CD8+ T cells [35,36]. MSCs also can express abundant Toll-like receptor (TLR) molecules—for example, TLR-3 and TLR-4—which activate nuclear factor κ B (NF- κ B) and subsequently enhance secretion of pro-inflammatory cytokines, including CXCL10, IL-6, and IL-8. TLR immune activation has inhibitory effect over MSC immunosuppression during RNA-virus and bacterial infections [37].

2.2. Tissue Protection and Regeneration

Others with immunomodulation, MSCs reduce the damage and restrict the repair of the tissue through paracrine actions on the endogenous recipient cells [38]. From hematology perspective, the most prominent feature of MSCs is being a potential regenerator for bone marrow stroma in poor graft function (PGF) [12].

MSCs exert a multifaceted therapeutic influence in the setting of poor graft function (PGF) following allogeneic hematopoietic stem cell transplantation. As essential components of the bone marrow microenvironment, MSCs provide structural and trophic support to hematopoietic stem and progenitor cells (HSPCs) through the secretion of stem cell factors (SCF), CXCL12, IL-6, and vascular endothelial growth factor (VEGF), all of which promote HSPC survival, homing, and proliferation [12]. In the context of PGF, where the stromal niche is often damaged or functionally exhausted, exogenously infused MSCs help restore stromal integrity and reconstitute the hematopoietic niche [12].

Beyond this supportive role, MSCs secrete angiogenic factors such as VEGF, hepatocyte growth factor (HGF), and angiopoietin-1, which facilitate endothelial repair and microvascular regeneration, thereby improving marrow perfusion and oxygenation [39]. Their potent immunomodulatory properties—marked by the suppression of alloreactive T cells and natural killer cells, expansion of

regulatory T cells, and modulation of cytokine networks toward an anti-inflammatory profile—further mitigate immune-mediated marrow injury [39]. In addition, MSC-derived paracrine signals and extracellular vesicles confer anti-apoptotic and anti-fibrotic effects by enhancing progenitor cell survival and remodeling the extracellular matrix. Collectively, these biological attributes enable MSCs to simultaneously repair the marrow microenvironment, rebalance immune homeostasis, and promote durable hematopoietic recovery, providing a strong mechanistic rationale for their therapeutic application in PGF [40,41].

3. Beyond the Cells: Exosomes

An exosome is a small, membrane-bound extracellular vesicle (EV) that is released by nearly all cell types into the extracellular environment [42]. Originally believed to be degrade plasma membrane, the immunological activities of exosomes were first demonstrated in 1996 by Raposo et al. showed that MHC II molecules on CD4⁺ T cells can present antigens to B cell-derived exosomes [43]. This momentous discovery underscored their significance in shaping adaptive immune responses and inspired hope of exosome-based immunotherapy.

Exosomes have key functions in intercellular communication via the delivery of proteins, lipids, mRNAs, and miRNAs between cells [43]. They are associated with a variety of physiological and pathophysiological conditions including cancer [44]. MSCs exert their immunomodulatory functions partly through their secretome, a complex mixture of cytokines, growth factors, chemokines, and extracellular vesicles (MSC-EVs) that collectively regulate immune cell behavior [9]. The MSC-derived vesicles modulate immune activity by suppressing Th17 differentiation and reducing the secretion of pro-inflammatory cytokines such as TNF- α , IL-17, IL-22, and IFN- γ [16]. Additionally, MSC-EVs promote peripheral immune tolerance through the expression of checkpoint molecules PD-L1 and PD-L2 [16].

4. MSCs for the Treatment of GVHD

The attack of the host tissues by donor T cells is known as GVHD and is a well-documented response following allogeneic HSCT. It is typically divided into acute (aGVHD) or chronic (cGVHD), depending on whether it occurs before or after post-transplant day 100, as historically defined [45]. Yet this distinction is arbitrary along the time axis, since aGVHD can continue over 100 days, and there is often an overlap between the acute and chronic form [45].

Graft-versus-host disease (GVHD) is initiated by tissue damage incurred by the conditioning, which liberates pro-inflammatory cytokines that serve prime donor T cells. These donor T cells respond to host major and minor histocompatibility antigens, migrate to target organs, and recruit effector cells, including cytotoxic T cells and NK cells. Effector cells induce tissue damage through either direct cytotoxicity and/or release of cytokines to augment inflammation. The skin, the GI tract, and the liver are the most frequently involved organs [46]. GVHD causes death in 8–16% of adult HSCT recipients [47], but this is likely an underestimation since GVHD increases the risk for secondary causes of death, i.e., infection, organ failure, and bleeding.

Chronic GVHD (cGVHD) is associated with persistent inflammation; elimination of tolerance; dysregulation of T cells and B cells, and defective regulatory subsets. Activated (i.e., matrix-producing) myofibroblasts, activated by cytokines such as platelet-derived growth factor α (PDGF α) and transforming growth factor β (TGF β), provoke fibrosis that can lead to involvement of multiple tissues. Cytokines such as inflammatory chemokines, CXCL9, CXCL10, and B-cell activating factor (BAFF) have shown to be increased in cGVHD [48]. Elevated CXCL9 at day +100 has been linked with progressive severe cGVHD, and elevated CXCL10 was described in patients with early rather than chronic manifestations [49]. Different metabolic profiles may be also useful to differentiate active inflammation from irreversible tissue destruction [50,51].

Corticosteroids continue to be the mainstay of primary treatment for aGVHD and cGVHD, although outcomes are mixed and poor in steroid-refractory patients [52]. Several other agents like

Janus Kinase (JAK) inhibitor ruxolitinib and Rho-associated coiled-coil containing protein kinase 2 (ROCK2) inhibitor belumosidil were demonstrated as effective options and was approved by the Food and Drug Administration (FDA) for acute and chronic forms of the disease [53,54]. Nevertheless, 50–60% of patients require additional “steroid-sparing” modalities at any point of the course [52].

Based on early in vitro evidence of the potent immunomodulatory properties of MSCs, their adoptive transfer was proposed for the treatment of steroid-refractory acute graft-versus-host disease (SR-aGVHD) [11]. The first successful case in 2004 showed resolution of severe gastrointestinal and hepatic GVHD after infusion of haploidentical maternal MSCs [11], followed by a European phase II trial in which 55 patients achieved an overall response (OR) rate of 71% with significantly improved survival among complete responders [55]. Subsequent meta-analyses confirmed the safety of systemic MSC therapy with minimal toxicity and no increased risk of relapse or malignancy, though occasional late infectious events were reported [56–60]. In later phase II–III studies, including a U.S. multicenter trial of Remestemcel-L (Prochymal), MSCs were well tolerated but failed to meet primary endpoints; subgroup analyses suggested higher response rates in liver GVHD and among pediatric patients [61,62]. Consistent findings were reported in European, Asian, and Chinese studies showing ORs of 48–71% and improved survival among responders [34,63–68]. Real-world data from Japan with Temcell demonstrated organ-specific ORs (36–64%) and highlighted favorable outcomes in younger patients and early intervention [69]. Collectively, these findings indicate that MSCs provide a safe adjunctive option for SR-aGVHD. A summary of relevant studies displayed in Table 1.

Table 1. MSC treatment studies with 25 participants or more.

Reference, year	Cohort	Acute GVHD grade	Dose of MSCs, cells/kg	Number of doses	Response rate Day +28	Survival
Le Blanc et al. 2008 [55]	n=55 (25 children, 30 adults)	II: n=5, III: n=25, IV: n=25	1.4×10 ⁶	1 (n=27), 2 (n=5), 3–5 (n=6)	CR=54.5%, PR=16%, OR=70.8%	2-year OS 35%
Resnick et al. 2013 [70]	n=50 (25 children, 25 adults)	II–III: n=8, IV: n=42	1.05×10 ⁶ (avg first dose)	1–6	CR=34%, PR=16%, OR=50%	3.6-year DFS 56%
Sánchez-Guijo et al. 2014 [68]	n=25 adults	II: n=7, III: n=15, IV: n=3	1.1×10 ⁶	2 (n=4), 3 (n=7), 4 (n=14)	CR=44%, PR=27%, OR=71%	1-year OS 40%
Introna et al. 2014 [71]	n=40 (15 children, 25 adults)	II–IV: n=20 GVHD overlap: n=20	1.5×10 ⁶	3 (children 2–7), 2 (adults 2–11)	CR=57.1%, PR=40%, OR=60%	2-year OS 50% children, 38.6% adults
Zhao et al. 2015 [65]	n=28 (age 14–54)	II: n=4, III: n=8, IV: n=16	1×10 ⁶	4 (2–8)	MSC vs. ctrl CR: 75% vs. 42%, OR: 60% vs. 26%	M vs. C 1-year OS: 46% vs. 26%, (1.1–5.4m)
Te Boome et al. 2015 [72]	n=48 (7 children, 41 adults)	II: n=3, III: n=33, IV: n=12	-	-	CR=25%	1-year OS 44%
von Dalowski et al. 2016 [73]	n=58 adults	II–III: n=12, IV: n=46	0.99×10 ⁶	≤2 (n=40), >3 (n=18)	CR=9%, PR=38%, OR=47%	100-day OS 34.5%, 2-year OS 16.6%
Fernández-Maqueda et al. 2017 [63]	n=33 adults	II: n=17, III: n=7, IV: n=9	1.06×10 ⁶	4 (1–16)	CR=33%, PR=48%, NR=15%	1-year OS 79% in CR patients vs. 25% in PR/NR

Salmenniemi et al. 2017 [66]	n=30 (8 children, 22 adults)	II: n=2, III: n=14, IV: n=14, 2×10 ⁶ cGVHD: n=4	Up to 6 doses	CR=23%, VGPR=13%, PR=17%, OR=53%	6-month OS 54%, 2-year OS 29%
Dotoli et al. 2017 [74]	n=46 (16 children, 30 adults)	II: n=10, III: n=20, IV: n=16	Cumulative dose 6.81×10 ⁶ 3 (1–7)	CR=6.5%, PR=43.5%, OR=50%	100-day OS 34.4%, 2-year OS 17.4%
Servais et al. 2018 [75]	n=33 (4 children, 29 adults)	II: n=5, III: n=15, 1–2×10 ⁶ , 3–4×10 ⁶ IV: n=13	1 (n=25), 2 (n=8)	CR=21.9%, OR=40%	1-year OS 18%
Bader et al. 2018 [56]	n=69 (51 children, 18 adults)	II: n=10, III: n=18, IV: n=41	1–2×10 ⁶ 1–4	CR=31.9%, PR=50.7%, OR=82.6%	6-month OS 71.6%
Galleu et al. 2019 [76]	n=60 (4 months–68 years)	II–III: n=5, IV–V: n=55	2.6×10 ⁶ 1 (n=34), 2 (n=16), 3 (n=6), NRe 6 (n=1)		OS 104 days (0–215)
Hinden L, et al. 2019 [77]	n=26 (both <18 and >18)	II: 3 responders, 2 non-responders, III–IV: 10 responders, 11 non-responders	0.59–1.8x 10 ⁶ 1 (n=26)	NRe	OS 40 days 11 (84.6% responders) and 4 (30.8% non-responders)
Kebriaei P, et al. 2020 [61]	n=163 with MSCs (M) and 81 controls (C)	II: 37 M, 21 C, III: 82 M, 44 C, IV: 44 M, 14 C	2×10 ⁶ 8 given over 4 weeks; PR maintained for an additional 4 weeks	DCR=38.5%, MCR=32.1, OR=53.8% M vs. 54.3% C	180 days M: 34% C: 42%
Kurtzberg J, et al. 2020 [78]	n=54	II: n=23, III: n=26, IV: n=5	2×10 ⁶ 8 given over 4 weeks	CR=25.9%, PR=40.7%, OR=66.6%	180 days, 68.5%
Ke Zhao et al. 2022 [79]	n=101 with MSCs (M) and n=102 controls without MSCs (C)	II:36M,37C III:41M,44C IV:22M,18C	1×10 ⁶ Once weekly for 4 consecutive weeks	CR=56.6%, PR=26.3% OR=82.9%	
Ruihao Huang et al.2024 Preemptive therapy after haplo HSCT [89]	n=74 with MSCs (M) and n=74 controls standard prophylaxis (C)	II:2M, III and IV n=10C	1 × 10 ⁶ 4(every 2 weeks)		2-year cumulative incidence of severe cGVHD in the M group n:4 and C group:13
Ulu et al.2025[80]	n=36 with MSCs	III and IV n=24	1.72x10 ⁶ 2(every 2 weeks)	PR+CR=20%	6-month OS 33.3%
Han Yao et al.2025 Preemptive therapy after haplo HSCT*[90]	n = 96 with MSCs (M) and 96 controls (C)	III and IV M group n=2 III and IV C group n:21	1 × 10 ⁶ 8 (eight doses within 3 months)		3-year GFRS rate in the M group n:59 and C group:30

Abbreviations: aGvHD, acute graft-versus-host disease; cGvHD, chronic graft-versus-host disease; GRFS,GVHD-free and relapse-free survival rate; MSCs, mesenchymal stem/stromal cells; OS, overall survival; DFS, disease-free survival; CR, complete response; DCR, durable complete response; MCR, major complete

response VGPR, very good partial response; PR, partial response; OR, overall response; NRe, not reported; M, MSC treatment arm; C, control arm.

5. MSC for the Treatment of Poor Graft Function

Poor graft function (PGF) is a rare yet serious complication following allogeneic hematopoietic cell transplantation (alloHCT), distinct from graft failure or GVHD. It is characterized by persistent cytopenia requiring frequent transfusions or growth factor support, despite full donor chimerism and the absence of relapse or other causes [81]. PGF leads to significant morbidity, including recurrent infections, bleeding, iron overload, and repeated hospitalizations [81,82]. Current management strategies—such as thrombopoietin receptor agonists (TPO-RAs), donor stem cell boosts, or second transplants—are often limited by inconsistent efficacy, treatment-related toxicity, and the risk of GVHD [83–85]. In this context, MSCs have emerged as a promising alternative. The bone marrow microenvironment is frequently damaged in transplant recipients due to underlying malignancy, conditioning therapy, or immune injury [85]. Since MSCs play a key role in maintaining hematopoietic homeostasis through secretion of cytokines and growth factors and by modulating immune responses, their use may restore stromal support and promote hematopoietic recovery in PGF [86].

Clinical studies have explored various strategies combining MSCs with other agents to improve hematopoietic recovery in PGF. In one study, Zhu et al. treated 16 patients with severe post-transplant thrombocytopenia using weekly infusions of umbilical cord–derived MSCs (1×10^6 cells/kg for 4–6 doses) plus avatrombopag, a second-generation thrombopoietin receptor agonist (TPO-RA), achieving platelet counts $>50 \times 10^9/L$ in 13 patients within a median of 32 days [87]. Similarly, a multicenter prospective trial using single or repeated intravenous infusions of third-party bone marrow–derived MSCs ($1\text{--}2 \times 10^6$ cells/kg) in 30 PGF patients produced complete hematologic responses in one-third of cases [12].

As of June 2021, 43 interventional or expanded-access MSC trials for GVHD had been registered on *clinicaltrials.gov*, including 19 completed and 10 with published outcomes. A broader review of 55 clinical studies encompassing 2,696 patients confirmed the excellent safety profile of MSC therapy, with only transient fever reported as a consistent adverse event and no observed increase in infusion-related toxicity, infection, thrombosis, death, or secondary malignancy [88].

6. Conclusions and Future Perspectives

Because of the multipotent nature and the immunomodulatory capacity of MSCs, they are highly promising for applications in regenerative medicine and immune-related diseases. These effects are mainly mediated by direct contact with immune cells along with paracrine action of chemokines, cytokines, growth factors, other inflammatory signals. Moreover, MSCs derived exosomes are an exciting therapeutic candidate, bearing the therapeutic attributes of their mother cells and with improved safety profile which minimizes concerns on tumorigenesis and genetic instability.

However, the clinical use of MSCs as a therapy is still at issue even though remarkable advances have been achieved. As of now, robust and conclusive evidence with respect to all patient cohorts has not been provided. Importantly, MSCs are heterogeneous, and their function mathematically modeled which depends greatly on anti-inflammatory as well as inflammatory microenvironments has been leading to the difference in immunomodulatory results. Acute and chronic inflammation-induced alterations of MSC function need to be further studied.

Problems remaining are the survival time and homing capacity of infused MSCs, which are determined by the local microenvironment around lesions. However, optimizing the preconditioning protocols for improving the therapeutic efficacy and paracrine stability of MSCs and maximizing their therapeutic effects is still a priority, especially in the clinical context of transplantation.

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